clinical trials, with complete baseline clinical, laboratory, and genetic characterization and detailed annotation of induction clinical course. Recently, the Ferrara criteria[1] have been shown to predict early post-treatment mortality and OS in a heterogenous group of myeloid neoplasm patients receiving several different intensive induction or re-induction regimens.[2] In contrast, our study focuses on a fit, previously-untreated cohort (where only two patients would be categorized as Ferrara-unfit) and thus addresses factors predictive of early mortality in the Ferrara-fit patients routinely offered intensive induction therapy given perceived favorable risk ratio.

Overall, our results indicate that distinct pretreatment characteristics predict early versus late adverse outcomes in fit patients with newly diagnosed AML. Improved ability to identify patients with high risk of early death after intensive AML induction may allow development of mitigation strategies. Unanswered questions include whether these fit patients who are at high risk for early mortality after intensive induction would have improved outcomes with alternative therapeutic approaches, or whether the risk of early mortality is inherent to disease biology at presentation. Further investigations into the molecular mechanisms of the gene mutations associated with early post-treatment mortality may yield novel mechanistic links between disease biology and adverse clinical outcomes in specific treatment contexts.

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AUTHORSHIP CONTRIBUTIONS

J.E.H., R.C.L., and M.R.L. designed the study, collected and assembled data, performed and interpreted data analyses, and wrote the manuscript. Y.F. and D.N. performed and interpreted statistical analyses. R.S.V. and J.V. contributed to study design, collected data, and participated in discussions of data analysis interpretation. R.M.S. and D.J.D. provided overall guidance, patient data, and edited the manuscript. A.C. and K.M.C. collected and assembled data.

CONFLICTS OF INTEREST

All authors declare no relevant conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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Seasonal variation in the incidence of cold agglutinin disease in Norway, Denmark, and Italy

To the Editor:

Cold agglutinin disease (CAD) is an autoimmune hemolytic anemia characterized by monoclonal autoantibodies targeting red blood cell

surface structures, showing a binding optimal temperature below 37°C. During cold weather, patients with CAD often suffer from increased hemolysis and may report worsening of symptoms such as acrocyanosis, dark urine, or Raynaud-like symptoms. The primary prophylaxis is to avoid exposure to low temperatures.[1,2]

Cold agglutinin disease is predominantly a disease of old age, and is extremely rare before 50 years.[1-4] Crude incidence rates vary across Europe.[1,3] The crude incidences in Denmark and Norway are comparable, with rates of 18 to 19/100 000 person-years, respectively.[1,3] Differently from these northern countries, the crude incidence rate in Lombardy, Italy, is only 4.8/100 000 person-years, despite a comparable or larger proportion of elderly.[1] A possible explanation could be the climatic differences, particularly considering outdoor temperature.[1,5] Cold weather could trigger symptoms that would lead to clinical examination and a subsequent diagnosis more often than warmer weather. To evaluate this proposed explanation we compared the monthly incidence of CAD in Norway, Denmark, and Lombardy expecting a seasonal pattern. We further compared with the monthly incidence of other acquired hemolytic disorders in Denmark to asses if a seasonal pattern was present in other acquired hemolytic conditions.

We obtained nationwide incidence information from Norway and Denmark, and region wide from Lombardy, Italy. Data from Norway included all patients diagnosed with CAD, 2007–2018[1]; from Denmark, all patients with CAD, 1994–2016,[3] and from Italy, Lombardy, all patients with CAD, 2007–2018.[1] We included all patients with other acquired hemolysis from the Danish Hemolysis Cohort, 1980–2016.[3,6]

We obtained local monthly mean temperature from publicly available sites. The mean temperature span in Norway is large and the country was therefore defined into two climatic areas: Mild Norway comprising coastal and southern parts, the monthly temperature was based on means from Bergen, Fredrikstad, Kristiansand, and Stavanger; Cold Norway comprising the northern and central part of Norway, temperature was based on Bodø, Oslo, and Trondheim. Denmark and Lombardy are climatically uniform and temperature was based on the available average measures.

The primary outcome was incidence of CAD per month. Secondary outcome was the comparison of CAD incidence with that of other acquired hemolytic anemias per month in Denmark.

To depict these outcomes we created graphs of CAD incidence per month for the five data sets: Norway, cold Norway, mild Norway, Denmark, and Lombardy in Italy, supplementing with the incidence in the combined mild climatic areas (mild Norway, Denmark, and Italy), and all areas combined. We further compiled graphs of the incidence of other acquired hemolytic anemias per month in Denmark.

We used Poisson regression to test the incidence of CAD in combined mild climate and all countries combined with month of diagnosis as exposure. We used robust standard errors to counteract mild violations of the underlying model assumptions.

In the Danish data, we were unable to distinguish CAD from the adjacent but distinctly different condition of cold agglutinin syndrome in which the autoantibodies occur secondary to an underlying disease.[1,3] As a sensitivity analysis, we therefor excluded all patients with CAD and a potential underlying disease of autoimmunity, chronic infections, hematological malignancies, or cancer, and reiterated all graphs and regressions. Diagnosis codes used for the exclusion is listed in Table S1.

We included 313 patients with CAD; 160 from Norway, mean age at diagnosis of 71.0 [95% CI: 69.0; 73.0] years; 112 from Denmark, mean age at diagnosis of 68.6 [95% CI: 65.8; 71.3] years, and 41 from Lombardy, Italy, mean age at diagnosis 63.0 [95% CI: 59.0; 66.9] years.

Further, 6016 patients with other acquired hemolytic anemias from Denmark were included: autoimmune hemolytic anemia, n = 2715; acquired hemolysis not otherwise specified, n = 2145; drug-induced hemolytic anemia, n = 397; Evans syndrome, n = 260 patients; paroxysmal nocturnal hemoglobinuria, n = 116 patients, and the less well-defined acquired hemolytic anemias, n = 374.

Figure 1(A) depicts the monthly incidence of CAD in Norway, Denmark, Italy, and all regions combined, along with the subdivided datasets from Norway, and the combined mild climatic areas. The decrease in incidence of CAD during summer and comparable higher incidence during winter is evident in all subgraphs. Although the decrease was less prominent in the colder part of Norway, a peak of incidence was still manifest in February, the coldest month. It is likely that the colder winter temperatures provoke latent disease to become apparent, thereby facilitating diagnosis.

The incidence rate ratio for combined mild climatic areas was between 0.7 and 1.1 from October to April, and below 0.5 from May to September, using January as reference (Table S2). Similar findings, although not statistically significant, were observed when cold climate Norway was included (Table S3). This is not unexpected given the lower temperatures during summertime in this region. Nevertheless, the number of diagnosed patients from cold climate Norway is small and the results could be susceptible to random variation.

Italy provides the most extreme seasonal difference in incidence. More than 50% of the cases are diagnosed in January, February, or December, and only 17% are diagnosed from May to September. This is probably related to the mild climate, although occasional exposure to cold temperatures (sea/lake water, or air conditioning) may still occur and cause symptoms.

The monthly variation in incidence of all acquired hemolytic disorders, including CAD in Denmark, is presented in the Figure 1(B). The lower incidence of CAD during summer is not reflected in any other acquired hemolytic disorders.

A possible bias of this analysis may be the decrease of diagnostic activity during the summer holidays. However, the period of decreased incidence is far longer than the summer holidays. Further, the data from Denmark concerning all other acquired hemolytic disorders do not reproduce this trend and make such bias unlikely. The decrease in incidence during summer does probably not reflect an absence of patients, but rather an absence of symptoms that lead the patient to seek medical attention.[1,2]

In the sensitivity analysis, we excluded 55 Danish patients with possible cold agglutinin syndrome. Even after this exclusion 53% of

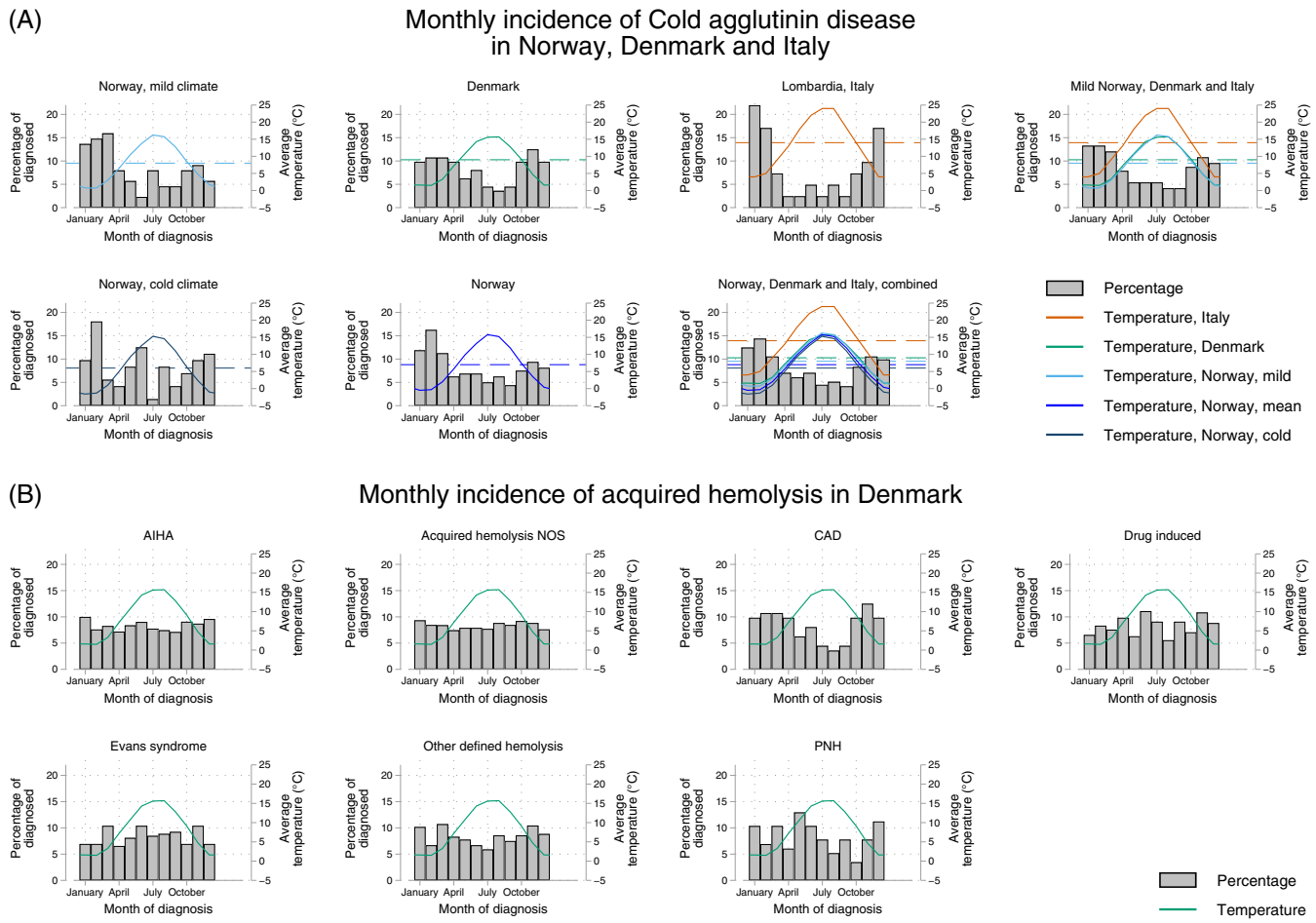

FIGURE 1 Monthly incidence of CAD in Norway, Denmark, and Italy, compared with incidence of acquired hemolysis in Denmark. (A) Distribution of patients newly diagnoses with cold agglutinin disease (CAD) by month of diagnosis in Norway, Denmark, and Lombardy in Italy. Norway is subdivided into mild Norway including the southern and coastal municipalities, and cold climate Norway being the remaining part of Norway. Solid lines represent the monthly average temperature in the countries. The dashed line represents the annual mean temperature. (B) Distribution of patients newly diagnoses with acquired hemolytic disorders by month of diagnosis in Denmark, 1980–2000. The solid turquoise lines represent the monthly average temperature in the Denmark. Abbreviations: AIHA, autoimmune hemolytic anemia; CAD, cold agglutinin disease; °C, degrees Celsius; NOS, not otherwise specified; PNH, paroxysmal nocturnal hematuria

the diagnoses were still made November through March (Figures S1 and S2). This exclusion is perhaps too extensive, as we cannot be sure of the relationship between the diagnoses. Further, it could be argued that even patients with cold agglutinin syndrome will probably only be diagnosed with cold antibodies if they have symptoms. The increased incidence during winter could potentially also be related to airway infections and increased complement production. However, as the Norwegian and Italian patients have been individually validated to exclude this and other underlying causes, this alternative explanation is unlikely.[1]

In conclusion, we report decreased incidence of CAD during summertime in Norway, Denmark, and Italy. The seasonal variation supports that temperature triggered symptoms are the driving cause for initiating the diagnostic process. However, patients in follow-up with chronic CAD may experience worsening of anemia and report ischemic symptoms even in the warm seasons due to various triggers (occasional exposure to low temperature or infections). Therefore, patient education concerning prophylaxis and symptoms recognition remains a cornerstone in the care of patients with CAD.

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AUTHOR CONTRIBUTIONS

D.L.H. and .P.L.H concocted the study. D.L.H., H.F., and S.B. planned analysis. S.B. provided Norwegian data. B.F. and W.B. provided Italian data. D.L.H. and H.F. provided Danish data. D.L.H. and H.F. wrote the first draft. All authors participated in revising and final approval of subsequent drafts.

DATA AVAILABILITY STATEMENT

Other laboratory or clinical data is available from the corresponding author on reasonable request.

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Survival of chronic myeloid leukemia patients in comparison to the general population in the tyrosine kinase inhibitors era: A US population-based study

To the Editor:

Treatment of chronic myeloid leukemia (CML) was revolutionized by the introduction of ABL tyrosine kinase inhibitors (TKIs) in 2001, leading many patients to achieve deep and even durable responses. Recent studies have suggested that a substantial subset of patients with CML, responding to TKIs, have a life expectancy approaching the general population.[1,2] However, those studies are somewhat limited by small sample size, possible selection bias, and/or a less diverse population. Moreover, recent analyses using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database found that many older adults diagnosed with CML had difficulty initiating TKI therapy, but those who received appropriate TKI therapy achieved near normal survival, underscoring the impact of real-world variables, including access to care.[3] In this context, we sought to compare the relative survival (RS) of patients with CML in the United States (US) during the TKI era, analyzing several sociodemographic factors.

We utilized the SEER 18 registries to select patients diagnosed with BCR-ABL positive CML (ICD-O-3 code 9875/3) between 2001 (introduction of TKIs) and 2014 (most recent year with follow up available). The SEER-18 registry includes cancer populations from Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, Alaska Native, Greater California, Kentucky, Louisiana, New Jersey, and Greater Georgia registries, representing 27.8% of the US population. For different subsets we described RS,